Application No. 10/762,964
Filed: January 22, 2004
TC Art Unit: 1618
Confirmation No.: 6339

REMARKS

Claims 1-19 are pending. Claims 1-10 and 12-18 are rejected. Claim 11 is allowable except for its dependency on a rejected base claim. Claim 1 is amended and new claim 19 is added herein.

Claim 1 has been amended to reword the claim for clarity. In particular, the amount of ionic dispersants, which was previously specified in terms of their normal concentration resulting from diluting the solid formulation with water, has been restated in terms of gram-equivalent amounts in the solid formulation. The amount recited in claim 1, less than 0.007 gram-equivalent weights of ionic dispersants per gram of barium sulfate, is recalculated from the 0.035N concentration and 0.5% w/v barium sulfate previously recited in claim 1. The amount recited in claim 19, less than 0.00117 gram-equivalent weights of ionic dispersants per gram of barium sulfate, is recalculated from the 0.35N concentration and 3% w/v barium sulfate previously recited in claim 1. The newly specified concentration limits for ionic dispersants is a mere mathematical rearrangement of parameters previously recited in claim 1. Moreover, the specification describes concentrations in units of normality (N), previously used in claim 1, as "gram-equivalent weights per L of suspension" at page 10, line 19. The amendment of claim 1 was arrived at by dividing the gram equivalent weight of ionic surfactant in 1 L of a 0.035N solution (i.e., 0.035 gram equivalents) by the amount of barium sulfate in 1 L of a 0.5% w/v barium sulfate solution (claim 1; 0.035 / 5 = 0.007) or a 3% w/v barium sulfate solution (claim 19; 0.035 / 30 = 0.00117). Thus, the limits of the amended claim

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are identical to the original limits, but merely expressed in different units, with the unit conversion pointed out in the specification. No new matter has been added.

Advisory Action

The Advisory Action mailed August 15, 2007 maintains that the amendments and arguments filed July 31, 2007 are insufficient to overcome the rejections because "[t]here are no amounts of the components specified in the solid formulation (i.e., barium sulfate, flocculant, ionic dispersant, etc.). The previously recited limitation specifying "wherein upon dilution . . ." was not given patentable weight. The recitation of "upon dilution" was interpreted as requiring a step that no longer resulted in a solid formulation.

With all due respect, Applicant continues to disagree with this line of thinking. Claim 1 has never recited a step, but merely a means of specifying the amount of ionic dispersant in the solid formulation. Applicant submits that this would be entirely clear to the ordinary skilled artisan as a way of expressing the upper limit for the ionic dispersant concentration of the claimed solid formulation, and not as reciting a liquid formulation, a method of producing a liquid formulation, or a product made by a certain process. In an effort to simplify the expression of the limit on ionic surfactant concentration in the claimed solid formulation, Applicant has now amended the claim to express the ionic surfactant concentration in terms of gram equivalents of ionic dispersant per gram of barium sulfate.

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The claim rejections have been previously addressed in Applicant's amendment filed on July 31, 2007. The following is a brief review, incorporating where appropriate the significance of the present amendment to the claims.

Claims 1-10 and 12-18 are rejected for alleged anticipation or obviousness. The claim rejections are respectfully traversed. In view of the amendments and the arguments below, all claims are believed to be allowable, and reconsideration of the rejections is hereby requested.

Rejection Under 35 U.S.C. 102(b)

Claims 1-4, 6-8, and 10 are rejected for alleged anticipation by Brown U.S. 3,236,735. Brown is cited as teaching solid formulations comprising barium sulfate and a flocculant. The distinction previously argued by Applicant regarding the low content of ionic dispersants required by the present claims was not given weight, because this was considered merely optional in view of the claim term "if".

Claim 1 has been amended to recite a solid stool marker formulation "wherein the amount of ionic dispersants in said solid stool marker formulation is less than 0.007 gram-equivalent weights of ionic dispersants per gram of barium sulfate". Thus, claim 1 as amended is clear in requiring the solid formulation to have at most a very low content of ionic dispersants. As argued previously, this alone should be sufficient to distinguish the claimed composition over the Brown compositions, which employ sufficient anionic dispersants to achieve barium distribution along the lining of the colon. The compositions of the present

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claims, however, limit the amount of anionic dispersants, and require sufficient flocculant, so that the barium is concentrated in the stool and serves as a stool marker, not a marker for the lining of the colon.

There are at least two differences in chemical composition between the Brown formulations and the formulations of the present claims. First, Brown uses an amount of anionic dispersant that is higher than recited by the present claims. And second, Brown does not teach or suggest the use of a flocculant in an amount required by the present claims.

Brown teaches the use of bentonite in barium sulfate compositions, but not as a flocculant. He teaches bentonite, especially combined with a dispersant such as sodium carboxymethylcellulose (CMC), as an anti-settling agent or an anti-caking agent. In fact, Brown specifically teaches away from using bentonite alone (i.e., without a dispersant) or in an amount that would cause flocculation in the intestine:

> The sodium CMC also enhances the effectiveness of bentonite as an anti-settling and anti-caking agent. Bentonite is a useful suspending agent for barium sulfate to retard settling of the barium sulfate prior to its administration. Unfortunately, it is not compatible with gastric secretions, and used alone or in large quantities it will increase flocculation of the barium sulfate in the intestine.

Brown at column 4, lines 51-57. Furthermore, the only specific formulation taught by Brown which includes bentonite is a liquid

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formulation (see Example 3 of Brown), in which case bentonite is used as an anti-settling agent in a dispersive formulation ("provides excellent coating of the colon") that includes sodium CMC as a dispersant.

The Advisory Action notes that Brown teaches the benefit of a dry formulation. However, this statement is misleading, because Brown teaches bentonite only for use as an anti-settling agent, which is a function only relevant to liquid formulations. The examples of solid formulations in Brown do not use bentonite because it makes no sense to add an antisettling agent to a solid formulation. Therefore, the statement in the Advisory Action that "a reference is not limited to what is taught by the examples" is also misleading. In this case, Brown teaches only one example with bentonite, which is a liquid formulation. Brown teaches only solid formulations without bentonite. This does not allow the Examiner to combine the bentonite of the liquid formulation with the solid formulations, particularly when Brown teaches bentonite only as an anti-settling agent, a function only relevant to liquid formulations.

In further contrast to Brown's dispersive formulations, the present claims require a solid formulation that will lead to flocculation in the intestine by virtue of reciting: "wherein 0.25 g of said solid stool marker formulation diluted with water to 50ml and titrated against 3.0% w/v ferrous sulfate at pH 5.0-5.5 has a flocculation resistance of less than 5ml." The relevance of the flocculation resistance value is not a mere assertion; it is demonstrated by data summarized in Table 1 of the present specification.

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Brown does not disclose a solid stool marker formulation comprising barium sulfate and a flocculant, wherein the amount of ionic dispersants in said solid stool marker formulation is less than 0.007 gram-equivalent weights of ionic dispersants per gram of barium sulfate, and wherein 0.25 g of said solid stool marker formulation diluted with water to 50ml and titrated against 3.0% w/v ferrous sulfate at pH 5.0-5.5 has a flocculation resistance of less than 5ml; therefore, Brown does not anticipate any of the present claims. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. 103(a)

Claims 1-4, 6-8, and 10-16 are rejected as allegedly obvious over Brown U.S. 3,236,735 in view of Queille U.S. 4,120,946. Brown is cited for the teachings described above, and Queille is cited for teaching a formulation including barium sulfate, xanthan gum, and citrate.

The Office Action acknowledges that the combination of Brown and Queille fails to teach the formulation of claim 11, containing barium sulfate, clay, xanthan gum, and citrate; however, the rejection has been maintained with respect to composition claims 1-4, 6-8, and 10.

The point of the Queille invention was "to provide pharmaceutical compositions for barium opacification of the digestive tract which are characterized by the fact they contain colloidal barium sulfate and a polyacrylamide in an aqueous vehicle." Queille at column 1, lines 57-61. Queille discloses only liquid (aqueous) formulations, not solid formulations.

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Queille also uses polyacrylamide as a suspension agent for barium and to promote the adherence of barium to the walls of the colon. Queille at column 2,lines 11-16. The Queille compositions are thus dispersive and not flocculating. As discussed above, Brown fails to teach or suggest a flocculating formulation of barium sulfate having at most a very low anionic dispersant content, as recited by claim 1.

Therefore, neither Brown nor Queille, either alone or in combination, teaches or suggests a solid stool marker formulation comprising barium sulfate and a flocculant, wherein the amount of ionic dispersants in said solid stool marker formulation is less than 0.007 gram-equivalent weights of ionic dispersants per gram of barium sulfate, and wherein 0.25 g of said solid stool marker formulation diluted with water to 50ml and titrated against 3.0% w/v ferrous sulfate at pH 5.0-5.5 has a flocculation resistance of less than 5ml. Claims 1-4, 6-8, and 10-16 are not obvious over Brown in view of Queille, and withdrawal of this rejection is respectfully requested.

Claims 1-10 and 12-16 are rejected as allegedly obvious over Brown U.S. 3,236,735 in view of Ruddy U.S. 5,466,440 and Weaver U.S. 3,935,099. The Office Action rejects Applicant's previous argument with respect to this rejection by stating that "Ruddy was used to show that barium sulfate having particle sizes within the claimed range and prepared via high shear is known in the art for imaging." Furthermore, the Office Action points out that Ruddy's composition appear not to require ionic dispersants, because they require only barium sulfate, a bioadhesive surfactant, a clay, and water. The Office Action also seems to imply that Weaver is cited

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merely to reach claim 9, which recites a formulation treated with sonication; the citation of Weaver also appears to relate to the interpretation that claim 1, as previously worded, was a product-by-process claim.

There are several distinctions between the formulations taught by Ruddy and the present claims. First, Ruddy teaches only liquid formulations, as stated in the Office Action and in Ruddy at column 3, line 67. Second, the Ruddy formulations include a bioadhesive surfactant. While the surfactant may be uncharged, it is nevertheless a dispersant and has "mucoadhesive properties," meaning that it has the ability to disperse barium sulfate within the gastrointestinal tract and adhere it to the mucosal lining. The inclusion of a surfactant with mucoadhesive properties is inconsistent with a formulation having an ability to flocculate barium sulfate and to serve as a stool marker. The inclusion of clay in the Ruddy formulations, together with a surfactant, is exactly analogous to Brown's use of bentonite together with an anionic dispersant. The clay is required as a suspending agent for barium sulfate, while either a nonionic surfactant or an ionic dispersant prevents the very flocculation which is required by the present claims and required for the formulation to function as a stool marker as opposed to a contrast agent for the colonic mucosal lining.

Even if the use of high shear as disclosed in Ruddy, or sonication as disclosed in Weaver, were relevant to some of the dependent claims, the combined teachings of Brown, Ruddy, and Weaver still does not teach or suggest the invention of claim 1 because the references, either singly or combined, fail to teach a

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solid barium sulfate formulation that would meet the flocculation resistance value which is required by all of the present claims. The withdrawal of this rejection is respectfully requested.

Claims 1-4, 6-8, 10, and 12-16 are rejected as allegedly obvious over Brown U.S. 3,236,735 in view of Kaufman U.S. 6,331,116. The Office Action rejects Applicant's previous argument of this rejection on the basis that the former "if" language of claim 1 was not effective as a limitation for the solid formulation. As the amendment of claim 1 should clarify, the solid formulation of claim 1 differs from Brown, as discussed above, and from Kaufman, which merely teaches virtual colonoscopy using a prior art barium sulfate solution but fails to teach or even suggest the use of a flocculant. Therefore, the Brown and Kaufman references, either singly or combined, fail to teach or suggest every limitation of the present claims, and fail to render the claims obvious. The withdrawal of the rejection is respectfully requested.

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The Examiner is encouraged to telephone the undersigned attorney to discuss any matter which would expedite allowance of the present application.

Respectfully submitted,

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